SUPPLEMENTAL MATERIAL

Cardiac mortality among 200,000 five-year survivors of cancer diagnosed aged 15-39 years: The Teenage and Young Adult Cancer Survivor Study

Henson, Cardiac mortality among teenagers and young adults

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Subject Codes: Mortality/Survival, Epidemiology, Risk Factors

Supplemental Table 1: First Primary Cancer Classification Detail –Modified from Birch et al [1]

First Primary Cancer Grouping	Specific Cancer Description
Breast	Breast
Testicular	Germ cell gonadal
	Other specified gonadal tumours
	Testicular
Cervix	Cervix
Melanoma	Melanoma & Naevi
Central Nervous System Tumours	Pilocytic astrocytoma
	Other specified astrocytoma
	Glioblastoma/anaplastic astrocytoma
	Astrocytoma NOS *
	Oligodendroglioma
	Other specified glioma
	Glioma, NOS
	Ependymoma
	Medulloblastoma
	Supratentorial PNET
	Craniopharyngioma
	Other Pituitary tumours
	Pineal tumours
	Choroid plexus tumours
	Meningioma
	CNS nerve sheath tumours
	Other specified CNS †
	Unspecified malignant CNS
	Unspecified benign CNS
	Other CNS
	Germ cell intracranial
Hodgkin	Hodgkin Disease (specified)
	Hodgkin Disease NOS
Non-Hodgkin Lymphoma	Specified NHL ‡
	Unspecified NHL
	Misc lymphoreticular neops NEC
Thyroid	Thyroid
Gastrointestinal	Colon & rectum
	Stomach
	Liver
	Pancreas
	Gastrointesinal tract (other)
Soft Tissue Sarcoma	Fibrosarcoma
	Malig fibrous histiocytoma
	Dermatofibrosarcoma
	Rhabdomyosarcoma
	Liposarcoma
	Leiomyosarcoma
	Synovial sarcoma
	Clear cell sarcoma
	Blood vessel tumours
	Nerve sheath tumours
	Alveolar soft part sarcoma
	Other Specified Soft Tissue Sarcoma
	Unspecified Soft Tissue Sarcoma
Ovary	Ovary
	Germ cell gonadal (if female)
	Other specified gonadal tumours(if female)
Bladder	Bladder
	Other bladder
Kidney and GU tract §	GU tract §
	Kidney
	GU tract (other)

	Wilms tumour
Head & Neck	Nasopharyngeal Other lip/oral cavity/pharynx Other Nasal cavity/middle ear
Leukaemia (excl. AML[||])	Acute Lymphoid Leukaemia Chronic Myeloid Leukaemia Other Lymphoid Leukaemia Other Myeloid Leukaemia Other Specified Leukaemia Other Unspecified Leukaemia
Bone Tumour	Osteosarcoma Chondrosarcoma Ewing sarcoma Ewing sarcoma NOT bone Ewing sarcoma site unspecified Other bone tumours specific Bone tumours unspecified
Acute Myeloid Leukaemia	Acute Myeloid Leukaemia
Lung	Trachea, bronchus & lung

[*] NOS = not otherwise specified
[†] CNS = central nervous system
[‡] NHL = non-Hodgkin lymphoma
[§] GU = genitourinary
[||] AML = acute myeloid leukaemia

Supplemental Table 2: Cardiac disease classification: ICD revision 9 and ICD revision 10

Cause of Death	ICD*-9	ICD*-10
All cardiac disease	**391, 392.0, 393-398, 402, 404, 410-414, 416, 420-429**	**I01, I02.0, I05-I09, I11, I13, I20-I25, I27.1-I27-9, I30-I52**
Cardiomyopathy/ congestive heart failure	391.2, 398.0, 398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 422, 425, 428, 429.0, 429.1, 429.3	I01.2, I09.0, I11.0, I13.0, I13.2, I40-I43, I50, I51.4-5, I51.7
Valvular heart disease	424	I34-I39
Rheumatic valvular heart disease	391.1, 394-397	I01.1, I05-I08, I09.1
Ischaemic heart disease	410-414, 429.7	I20-I25
Arrhythmias	426-427	I44-49
Pericardial disease	391.0, 393, 420, 423	I01.0, I09.2, I30-I32

* ICD = International Classification of Diseases

Supplemental Table 3: Relative risks (RR) and excess mortality ratios (EMR) relating to age at cancer diagnosis and first primary cancer type from a multivariable Poisson regression model adjusted for the specified potential confounders [,††] (corresponding to Table 2 and Table 3)**

Multivariable model		All cardiac disease RR [†] (95% CI [‡])	All cardiac disease EMR [§] (95% CI)	Ischaemic Heart Disease RR (95% CI)	Ischaemic Heart Disease EMR (95% CI)	Valvular HD RR(95% CI)	Valvular HD EMR (95% CI)	Cardiomyopathy / CHF * RR (95% CI)	Cardiomyopathy / CHF * EMR (95% CI)
Age at Cancer Diagnosis **	15-19	**(ref)** [‖]	**(ref)**	**(ref)**	**(ref)**	**(ref)**	**(ref)**	**(ref)**	**(ref)**
	20-24	0.7 (0.5,0.9)	0.8 (0.5,1.1)	0.8 (0.6,1.1)	1.2 (0.8,2.0)	0.5 (0.2,1.1)	0.5 (0.2,1.2)	0.7 (0.4,1.4)	0.7 (0.2,2.3)
	25-29	0.6 (0.4,0.7)	0.7 (0.5,1.0)	0.7 (0.5,0.9)	1.1 (0.7,1.9)	0.3 (0.1,0.7)	0.3 (0.1,0.7)	0.7 (0.4,1.4)	0.6 (0.2,1.9)
	30-34	0.5 (0.4,0.6)	0.6 (0.4,0.9)	0.6 (0.4,0.8)	1.1 (0.6,1.9)	0.2 (0.07,0.4)	0.4 (0.0,0.2)	0.9 (0.5,1.6)	1.3 (0.4,3.6)
	35-39	0.5 (0.4,0.6)	0.6 (0.4,0.9)	0.6 (0.4,0.8)	1.2 (0.7,2.2)	0.1 (0.1,0.3)	0.2 (0.0,0.4)	0.8 (0.4,1.5)	0.8 (0.3,2.6)
	2p for trend:	*<0.0001*	*0.02*	*0.001*	*0.67*	*<0.0001*	*<0.0001*	*0.85*	*0.76*
First Primary Cancer [††]	Breast	0.3 (0.2,0.3)	0.1 (0.0,0.2)	0.3 (0.2,0.4)	0.1 (0.05,0.2)	0.1 (0.05,0.3)	-	0.2 (0.1,0.4)	0.0 (0.0,0.5)
	Testicular	0.3 (0.3,0.4)	0.0 (0.0,0.5)	0.3 (0.3,0.4)	-	0.3 (0.1,0.6)	0.2 (0.09,0.6)	0.4 (0.2,0.6)	-
	Cervix	0.3 (0.2,0.3)	0.06 (0.0,0.2)	0.3 (0.3,0.4)	0.1 (0.05,0.2)	0.1 (0.06,0.3)	-	0.2 (0.1,0.3)	-
	Melanoma	0.1 (0.1,0.2)	- [‡‡]	0.1 (0.09,0.2)	-	0.07 (0.02,0.2)	-	0.2 (0.1,0.4)	-
	Central Nervous System Tumours	0.4 (0.3,0.4)	0.1 (0.1,0.3)	0.4 (0.3,0.5)	0.1 (0.07,0.3)	0.2 (0.08,0.5)	0.1 (0.0,0.5)	0.4 (0.2,0.7)	0.2 (0.1,0.7)
	Hodgkin	**(ref)**	**(ref)**	**(ref)**	**(ref)**	**(ref)**	**(ref)**	**(ref)**	**(ref)**
	Non-Hodgkin Lymphoma	0.5 (0.4,0.6)	0.3 (0.2,0.5)	0.5 (0.4,0.6)	0.3 (0.2,0.5)	0.2 (0.08,0.7)	0.2 (0.04,0.8)	0.8 (0.5,1.4)	0.6 (0.2,1.5)
	Thyroid	0.2 (0.2,0.3)	0.0 (0.0,0.4)	0.2 (0.2,0.3)	-	0.2 (0.09,0.7)	0.2 (0.03,0.9)	0.3 (0.1,0.7)	0.1 (0.01,1.2)
	Gastrointestinal	0.3 (0.2,0.3)	-	0.3 (0.2,0.4)	-	0.2 (0.05,0.5)	-	0.4 (0.2,0.9)	-
	Soft Tissue Sarcoma	0.3 (0.2,0.4)	0.1 (0.0,0.3)	0.3 (0.2,0.4)	-	0.1 (0.03,0.5)	0.1 (0.01,0.8)	0.8 (0.4,1.5)	0.7 (0.3,1.8)
	Ovary	0.2 (0.1,0.3)	-	0.2 (0.1,0.3)	-	0.1 (0.03,0.6)	-	0.4 (0.2,1.0)	0.2 (0.0,1.2)
	Bladder	0.3 (0.3,0.4)	0.0 (0.0,0.4)	0.3 (0.3,0.4)	-	0.2 (0.05,0.6)	0.1 (0.002,3.4)	0.2 (0.1,0.6)	0.1 (0.0,2.3)
	Kidney and GU tract [#]	0.6 (0.4,0.7)	0.5 (0.3,0.8)	0.6 (0.5,0.8)	0.6 (0.4,0.9)	0.4 (0.1,1.0)	0.3 (0.09,1.4)	0.5 (0.2,1.0)	0.3 (0.1,1.3)
	Head & Neck	0.3 (0.3,0.5)	0.1 (0.0,0.6]	0.4 (0.3,0.5)	0.0 (0.0,546.3)	0.1 (0.01,0.7)	0.0 (0.0,484.6)	0.3 (0.1,0.9)	0.2 (0.0,1.7)
	Leukaemia (excl. AML) [##]	0.4 (0.3,0.6)	0.2 (0.1,0.6)	0.4 (0.3,0.7)	0.2 (0.1,0.7)	0	-	0.5 (0.1,1.5)	0.3 (0.0,3.0)
	Other	0.4 (0.3,0.6)	0.2 (0.1,0.5)	0.4 (0.3,0.6)	0.2 (0.1,0.6)	0.2 (0.05,1.0)	0.2 (0.02,1.3)	0.5 (0.2,1.4)	0.5 (0.1,2.0)
	Bone Tumour	0.3 (0.2,0.5)	0.1 (0.0,0.6)	0.3 (0.2,0.6)	0.1 (0.0,1.1)	0.2 (0.03,1.5)	-	0.4 (0.09,1.6)	0.1 (0.0,78.2)
	Acute Myeloid Leukaemia	0.7 (0.4,1.1)	0.5 (0.2,1.2)	0.5 (0.2,1.0)	0.3 (0.0,1.5)	0.6 (0.08,4.5)	0.6 (0.06,6.1)	2.1 (0.9,4.9)	1.9 (0.7,5.6)
	Lung	0.5 (0.4,0.8)	0.5 (0.3,1.0)	0.5 (0.4,0.8)	0.4 (0.2,1.1	0.5 (0.1,2.3)	0.7 (0.1,3.3)	0.9 (0.3,2.5)	1.1 (0.3,4.2)
	2p for heterogeneity:	*<0.0001*	-	*<0.0001*	-	*<0.0001*	-	*<0.0001*	-

[*] CHF = congestive heart failure

[†] RR = relative risks – can be interpreted as ratios of standardised mortality ratios adjusted for confounding risk factors included in the model

[‡] CI = confidence interval

[§] EMR = excess mortality ratio - can be interpreted as ratios of absolute excess risks adjusted for confounding risk factors included in the model

[‖] ref = reference group

[#] GU = genitourinary
[##] AML = acute myeloid leukaemia
[**] adjusted for gender, decade of cancer diagnosis, first primary cancer type and attained age
[††] adjusted for gender, age at cancer diagnosis, decade of cancer diagnosis and attained age
[‡‡] unreliable model fit due to small numbers of events

Supplemental Table 4: Relative risks (RR) and excess mortality ratios (EMR) after specific cancers in relation to gender, age at cancer diagnosis, decade of cancer diagnosis and attained age from a multivariable Poisson regression model adjusted for the specified confounders [##,,††,‡‡] (corresponding to Table 4)**

Multivariable model	Hodgkin lymphoma		Non-Hodgkin lymphoma		Central Nervous System Tumours		Cervical Cancer		Breast cancer	
	RR [*] (95% CI [†])	EMR [‡] (95% CI)	RR (95% CI)	EMR (95% CI)	RR (95% CI)	EMR (95% CI)	RR (95% CI)	EMR (95% CI)	RR (95% CI)	EMR (95% CI)
Gender [##]										
Male	**(ref) [§]**	**(ref)**	**(ref)**	**(ref)**	**(ref)**	**(ref)**	-	-	-	-
Female	1.7 (1.4,2.1)	0.5 (0.4,0.7)	1.8 (1.2,2.7)	0.9 (0.4,1.9)	1.3 (0.9,1.9)	0.5 (0.2,1.5)	-	-	-	-
2p for het	*<0.0001*	*<0.0001*	*0.007*	*0.74*	*0.11*	*0.21*	-	-	-	-
Age at Cancer Diagnosis [**]										
15-19	**(ref)**	**(ref)**	**(ref)**	**(ref)**	**(ref)**	**(ref)**			-	-
20-24	0.6 (0.4,0.8)	0.7 (0.5,1.0)	2.3 (0.5,10.8)	[-#]	0.9 (0.3,2.5)	0.8 (0.0,13.2)	-	-	(ref)	(ref)
25-29	0.4 (0.3,0.5)	0.5 (0.3,0.7)	1.9 (0.4,8.5)	-	1.2 (0.5,3.0)	3.2 (0.5,22.9)	(ref)	(ref)	0.4 (0.1,1.4)	0.4 (0.1,2.2)
30-34	0.3 (0.2,0.5)	0.5 (0.3,0.8)	2.2 (0.5,9.3)	-	0.8 (0.3,2.1)	1.3 (0.1,25.0)	1.9 (1.0,3.6)	-	0.3 (0.1,1.0)	0.1 (0.0,1.0)
35-39	0.3 (0.2,0.4)	0.6 (0.4,0.9)	1.5 (0.3,6.5)	-	1.0 (0.4,2.5)	3.2 (0.2,43.2)	1.7 (0.9,3.4)	-	0.3 (0.1,0.8)	0.1 (0.0,0.8)
2p for trend	*<0.0001*	*0.01*	*0.40*	-	*0.89*	*0.25*	*0.30*	-	*0.08*	*0.06*
Decade of Cancer Diagnosis [††]										
1970-79	**(ref)**	**(ref)**	**(ref)**	**(ref)**	**(ref)**	**(ref)**	**(ref)**	**(ref)**	**(ref)**	**(ref)**
1980-89	0.7 (0.6,0.9)	0.4 (0.3,0.6)	1.0 (0.6,1.5)	0.5 (0.2,1.5)	1.3 (0.9,1.9)	2.3 (0.3,18.9)	1.0 (0.7,1.4)	1.2 (0.2,7.1)	1.5 (1.1,2.0)	1.9 (0.5,6.8)
1990-99	0.8 (0.6,1.1)	0.4 (0.2,0.6)	1.2 (0.7,2.0)	0.7 (0.3,1.9)	1.3 (0.8,2.2)	1.4 (0.1,14.4)	0.8 (0.5,1.5)	0.4 (0.0,4.4)	0.9 (0.5,1.4)	-
2000+	1.1 (0.6,2.1)	0.4 (0.2,0.9)	0.6 (0.2,1.9)	0.1 (0.0,2.8)	1.3 (0.5,3.3)	1.3 (0.1,18.5)	0.6 (0.1,2.4)	-	0.6 (0.2,1.6)	0.2 (0.0,37.8)
2p for trend	*0.11*	*<0.0001*	*0.95*	*0.15*	*0.27*	*0.93*	*0.48*	-	*0.87*	-
Attained Age [‡‡]										
20-39	**(ref)**	**(ref)**	**(ref)**	**(ref)**	**(ref)**	**(ref)**	**(ref)**	**(ref)**	**(ref)**	**(ref)**
40-49	1.0 (0.7,1.3)	3.6 (2.4,5.5)	0.8 (0.4,1.7)	2.2 (0.6,7.6)	0.5 (0.3,1.0)	0.7 (0.1,4.3)	0.5 (0.2,1.4)	0.8 (0.1,5.0)	0.6 (0.2,1.7)	2.1 (0.3,14.7)
50-59	0.9 (0.6,1.2)	6.6 (4.2,10.3)	0.6 (0.2,1.2)	1.9 (0.4,9.1)	0.5 (0.3,1.0)	1.4 (0.2,9.4)	0.4 (0.2,1.1)	0.8 (0.1,6.5)	0.4 (0.2,1.2)	0.3 (0.0,245.4)
60+	0.8 (0.6,1.2)	12.5 (7.4,21.1)	0.6 (0.2,1.4)	6.4 (1.4,29.6)	0.4 (0.2,0.9)	1.6 (0.1,25.5)	0.4 (0.1,1.0)	1.1 (0.1,17.7)	0.5 (0.2,1.3)	5.4 (0.6,46.4)
2p for trend	*0.24*	*<0.0001*	*0.19*	*0.05*	*0.11*	*0.56*	*0.08*	*0.99*	*0.20*	*0.58*

[*] RR = relative risks – can be interpreted as ratios of standardised mortality ratios adjusted for confounding risk factors included in the model

[†] CI = confidence interval

[‡] EMR = excess mortality ratio – can be interpreted as ratios of absolute excess risks adjusted for confounding risk factors included in the model

[§] ref = reference group

[#] unreliable model fit due to small numbers of events
[##] adjusted for age at cancer diagnosis, decade of cancer diagnosis, first primary cancer type and attained age
[**] adjusted for gender, decade of cancer diagnosis, first primary cancer type and attained age
[††] adjusted for gender, age at cancer diagnosis, first primary cancer type and attained age
[‡‡] adjusted for gender, age at cancer diagnosis, decade of cancer diagnosis and first primary cancer type

Supplemental Table 5: Total excess cardiac deaths as a proportion of total excess deaths for all cancers combined and specific first primary cancers subdivided by attained age

	AER * cardiac / AER all causes (%) by attained age								Total AER (%)	
	20-39		40-49		50-59		60+			
Hodgkin Lymphoma	3.9/75.9	(5.2%)	12.0/75.3	(15.9%)	24.9/118/3	(21.0%)	52.8/191.9	(27.5%)	12.9/89.0	(14.5%)
Non-Hodgkin Lymphoma	1.6/76.6	(2.1%)	4.2/130.8	(3.2%)	5.0/105.6	(4.7%)	14.4/101.5	(14.2%)	4.4/107.2	(4.1%)
Central Nervous System Tumours	1.3/181.8	(0.7%)	1.2/162.2	(0.8%)	2.6/95.8	(2.7%)	0.7/83.5	(0.8%)	1.5/150.4	(1.0%)
Cervical Cancer	0.4/38.9	(1.0%)	0.6/37.0	(1.5%)	1.0/33.8	(3.0%)	2.1/65.6	(3.1%)	0.8/39.7	(2.1%)
Breast Cancer	1.2/359.6	(0.3%)	0.7/258.5	(0.3%)	0.5/130.4	(0.3%)	2.4/86.4	(2.8%)	0.9/205.8	(0.4%)
All Cancers Combined	**1.3/91.5**	**(1.4%)**	**1.9/103.5**	**(1.8%)**	**2.2/67.1**	**(3.3%)**	**2.9/66.8**	**(4.3%)**	**1.9/88.3**	**(2.2%)**

* AER = absolute excess risk

Supplemental Reference

1. Birch JM, Alston RD, Kelsey AM, Quinn MJ, Babb P, McNally RJQ. Classification and incidence of cancers in adolescents and young adults in England 1979-1997. *Br J Cancer*. 2002; 87: 1267-74.